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COMPANY NOTE | EQUITY RESEARCH | July 31, 2024

Healthcare: Biotechnology

Company Update
Estimates Changed

Oryzon Genomics SA | ORY.SM-€1.88-MADRID | *Buy*

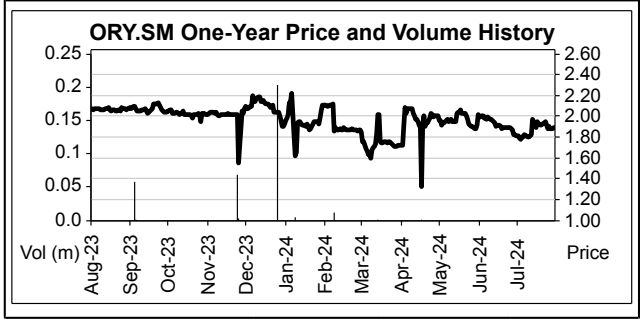
Stock Data	
52-Week Low - High	€1.41-€2.44
Shares Out. (mil)	64.01
Mkt. Cap.(mil)	€129.89
3-Mo. Avg. Vol.	0
12-Mo.Price Target	€12.00
Cash (mil)	€10.1
Tot. Debt (mil)	€18.1

Rev ($M)

Yr Dec	— 2023—	— 2024E—	— 2025E—
		Curr	Curr
1Q	0.0A	0.0A	-
2Q	0.0A	0.0A	-
3Q	0.0A	0.0E	-
4Q	0.0A	0.0E	-
YEAR	0.0A	0.0E	0.0E

EPS $

Yr Dec	— 2023—	— 2024E—		— 2025E—	
		Curr	Prev	Curr	Prev
1Q	(0.03)A	(0.02)A	(0.02)A	-	-
2Q	0.02A	0.00A	0.00A	-	-
3Q	(0.02)A	(0.02)E	(0.01)E	-	-
4Q	(0.03)A	(0.02)E	(0.01)E	-	-
YEAR	(0.06)A	(0.06)E	(0.04)E	(0.10)E	(0.06)E
P/E	NM	NM	NM	NM	NM



ORY 2Q24: PORTICO EOP2 Meeting Near Term, Three Trials Ongoing, Funded Thru 1Q25

ORY ended 2Q24 with USD$10.8M, enough to fund operations through 1Q25, and ORY has access to additional convertible debt financing. ORY is enrolling three trials, and expects to initiate six more trials. ORY believes that the FRIDA trial, which is its central iadademstat strategy, is iadademstat's fastest route to market. The FRIDA, SCLC basket, and EVOLUTION trials are enrolling, with enrollment still to start for five more iadademstat trials and the HOPE trial. PORTICO's EOP2 meeting for vafidemstat is granted, but timing is not disclosed.

Vafidemstat

- **PORTICO trial.** In 1Q24, PORTICO showed vafidemstat to be safe, but the trial failed to achieve its primary endpoints, namely the Borderline Personality Disorder Checklist (BPDCL) and the Clinical Global Impressions-Severity focused on Agitation/Aggression (CGI-S A/A) across weeks 8-12, both primary endpoints. Although there was a consistent reduction with vafidemstat versus placebo throughout treatment, statistical significance was not achieved (p=0.41 and p=0.25, respectively). As BPD has no well-established trial endpoints, two of PORTICO's secondary endpoints, which were achieved, will help inform the design of a registrational Phase 3 trial. Given that all 11 primary and secondary efficacy endpoints favored vafidemstat over placebo indicates that there is a positive treatment effect and that further clinical investigation is warranted, especially in a disease with no approved therapy. PORTICO (n=210; 27 U.S and European sites) is the first large, randomized Phase 2 BPD trial that statistically achieved two secondary endpoints that reflect clinically meaningful improvements in overall BPD severity and in agitation/aggression. We expect two Phase 3 trials of about 400 patients per trial to be conducted. ORY has been granted an EOP2 meeting by the FDA (time not released) given that its full PORTICO data analysis has been conducted, and a full analysis will be presented at September's European College of Neuropsychopharmacology annual conference. We note that 18 BPD trials have failed, and that with no available treatment and no established endpoints, using different primary endpoint(s) is a fair modification.
- **EVOLUTION trial.** The Phase 2b EVOLUTION trial evaluating vafidemstat in schizophrenia continues to enroll patients in Spain and is looking to establish vafidemstat efficacy on negative symptoms and cognitive impairment in patients with schizophrenia. EVOLUTION is partially funded by the Spanish Ministry of Science.
- **HOPE trial.** ORY is working with KOLs to finalize the design of HOPE, a randomized, double-blind, placebo-controlled, 50-60 patient Phase 1/2 personalized medicine trial with vafidemstat in Kabuki Syndrome patients. ORY is talking to regulatory agencies to refine the final design of HOPE, and may file an IND as early as YE24 in the U.S. *(text continues on page 2)*

Iadademstat

- **FRIDA trial.** ORY continues to enroll patients in its Phase 1b FRIDA trial in rel/ref AML with FLT3 mutations, which is evaluating iadademstat plus gilteritinib in up to 45 patients in the U.S. at up to 15 centers. FRIDA has primary endpoints of safety, tolerability, and determining the RP2D, and secondary endpoints of efficacy (i.e., CR/CRh, DoR, MRD), and ORY will meet with the FDA to best plan development of this combination therapy, if FRIDA is successful. ORY believes that the FRIDA trial, which is its central strategy, is iadademstat's fastest route to market. The first two dose escalation cohorts (13 patients total) are completed with no DLTs yet observed, and strong efficacy was observed. The third dose cohort is recruiting. At EHA-2024, ORY presented preliminary data from the first two dose cohorts of the trial (n=13 for efficacy, n=15 for safety). The therapy was safe (no DLTs thus far), well-tolerated, and had strong efficacy, given that nine (69%) had bone marrow blast clearance in the first cycle, including five (38%) patients achieving CR/CRh/CRi, and two underwent HSCT (highly favorable outcome in AML). Cohort 3 (lower iadademstat dose) is now enrolling, per FDA's Project Optimus guidelines.
- **First-line AML trial.** Iadademstat in combination with venetoclax and azacitidine will also be evaluated in first-line AML in a 45-patient Phase 1b dose-finding investigator-initiated trial led by the University of Pittsburgh Cancer Institute. The trial has FDA IND approval and should start enrolling patients later this quarter. This same triple combination therapy will also be evaluated in first-line AML in an Investigator-initiated study led by Oregon Health & Science University. The Phase Ib dose-finding study is open for recruitment and should begin enrolling patients later this quarter. In a related condition called myelodysplastic syndrome (MDS), ORY will evaluate iadademstat in a new Investigator-initiated study led by the Medical College of Wisconsin, which will evaluate iadademstat plus azacitidine in MDS.
- **SCLC basket trial.** ORY is also conducting a collaborative Phase 2 basket trial in the U.S. of iadademstat in combination with synergistic agents, such as paclitaxel, in platinum rel/ref SCLC and extrapulmonary high-grade neuroendocrine tumors. The first patient was enrolled in January 2023 and enrollment continues. The trial is being conducted in collaboration with Fox Chase Cancer Center, which will test iadademstat in combination with different therapies in trials funded by ORY.
- **MSKCC-led SCLC trial.** A new Phase 1/2 trial to evaluate iadademstat plus a checkpoint inhibitor in first-line metastatic SCLC, will be conducted under ORY's CRADA which was signed with the NCI and is under preparation. MSKCC will lead the trial and the IND was recently approved. About 45-50 patients will be enrolled and the trial should start enrolling later this quarter.
- **STELLAR trial.** ORY's Phase 2 STELLAR trial in the U.S. in first-line metastatic SCLC is being designed, and it is a randomized, multi-center trial of iadademstat plus a checkpoint inhibitor in this setting that could potentially support accelerated approval. We expect STELLAR to start once enough data from the other SCLC trial has been obtained to best inform the design of STELLAR.

Earlier-stage programs

- In 1Q23, ORY announced that it selected ORY-4001, a selective HDAC-6 inhibitor, as its drug candidate to bring into the clinic for neurological diseases such as Charcot-Marie-Tooth (CMT) and ALS, among others. HDAC-6 inhibitors are believed to be potentially effective treatments for CMT, ALS, and other neurological disorders lacking effective treatments. Last year, ORY and the CMT Research Foundation agreed to explore ORY's HDAC-6 inhibitors, and ORY-4001 was selected due to the positive preclinical results generated under this collaboration. ORY-4001 is highly selective against other HDAC classes, resulting in a favorable safety profile that avoids hematoxicity, as well as being strongly anti-inflammatory in vivo. ORY-4001 has shown multiple positive responses in a validated CMT1A peripheral neuropathy in vivo model which reliably recapitulates many of the symptoms of CMT in humans, and it is currently progressing through IND enabling studies. CMT is a progressive, degenerative peripheral nerve disease affecting 150k U.S. patients and over 3M globally. CMT is caused by a variety of genetic mutations, with CMT1A mutation causing the disease in about half of the patients. HDAC6 inhibition or depletion has also been previously described as a potentially effective treatment for ALS, protecting against neurodegeneration in various ALS mouse and human iPSC models. Due to the key role altered axonal transport and proteostasis play in both CMT and ALS, ORY will evaluate ORY-4001 in ALS mouse models. To help fund preclinical evaluation of ORY-4001 in ALS, the ALS Association has awarded ORY an almost $500k grant through its Lawrence and Isabel Barnett Drug

VALUATION

Our 12-month price target of €12, is based on a DCF analysis using a 35% discount rate that is applied to all cash flows and the terminal value, which is based on a 4x multiple of our projected 2030 operating income of $662 million. We arrive at this valuation by projecting future revenue from vafidemstat in borderline personality disorder and Kabuki syndrome, as well as iadademstat in AML and SCLC.

Factors that could impede shares of ORY.SM from achieving our price target include vafidemstat and iadademstat failing to generate statistically significant clinical results. Also, regulatory agencies could fail to approve these drugs even if pivotal clinical trials are statistical successes, due to the agency viewing the results as not clinically meaningful. Loss of key management personnel could also impede achieving our price target, as could smaller than projected commercial opportunity due to changes in market size, competitive landscape, and drug pricing and reimbursement.

RISKS

- **Clinical risk.** ORY.SM's clinical staged products could fail to deliver statistically significant results in late-stage clinical trials, substantially reducing the value of ORY.SM's product candidates and therefore our target price.
- **Regulatory risk.** Even if successful in the clinic, ORY.SM's products could fail to be approved by domestic and/or foreign regulatory bodies, which would reduce ORY.SM's value and therefore our target price.
- **Financing risk.** ORY.SM will need additional capital to fund its operations, and such financing may not occur, or it could be substantially dilutive to existing investors.
- **Competitive risk.** For any future approved ORY.SM products, they may not be well adopted in a competitive marketplace, which would adversely affect ORY.SM's value and therefore our target price.
- **High stock price volatility.** This issue is common among small-cap biotechnology companies with relatively low trading volumes.

COMPANY DESCRIPTION

Founded in 2000 in Barcelona, Spain, Oryzon (ISIN Code: ES0167733015) is a clinical stage biopharmaceutical company and the European leader in epigenetics, with a strong focus on personalized medicine in CNS disorders and oncology. Oryzon's team is composed of highly qualified professionals from the pharma industry located in Barcelona, Boston, and San Diego. Oryzon has an advanced clinical portfolio with two LSD1 inhibitors, vafidemstat in CNS and iadademstat in oncology, in several Phase II clinical trials. The company has other pipeline assets directed against other epigenetic targets like HDAC-6 where a clinical candidate ORY-4001, has been nominated for its possible development in CMT and ALS. In addition, Oryzon has a strong platform for biomarker identification and target validation for a variety of malignant and neurological diseases. For more information, visit www.oryzon.com

Oryzon Genomics SA
Income Statement
Fiscal Year ends December
(in 000, except per share items)

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	2018A	2019A	2020A	2021A	2022A	1Q23	2Q23	3Q23	4Q23	2023A	1Q24A	2Q24A	3Q24E	4Q24E	2024E	2025E	2026E	2027E	2028E	2029E	2030E
Global iadademstat revenue																-	7,683	99,008	147,956	176,048	184,560
Global vafidemstat revenue																-	-	156,140	322,805	477,033	530,992
Total revenue																-	**7,683**	**255,148**	**470,761**	**653,080**	**715,553**
Cost of revenue																-	1,153	17,570	26,435	30,024	30,193
R&D	8,489	12,647	13,591	15,118	17,701	4,372	4,264	3,821	3,867	16,324	2,636	2,325	2,348	2,372	9,681	11,133	11,690	11,807	11,925	12,044	12,164
G&A	2,993	3,176	3,484	5,529	4,771	1,223	1,096	674	1,187	4,180	863	1,222	1,100	1,111	4,296	4,725	8,033	8,836	9,720	10,206	10,716
Total operating expenses	**11,482**	**15,823**	**17,075**	**20,647**	**22,472**	**5,595**	**5,360**	**4,495**	**5,054**	**20,504**	**3,499**	**3,547**	**3,448**	**3,483**	**13,977**	**15,858**	**20,875**	**38,213**	**48,080**	**52,274**	**53,073**
Operating income	**(11,482)**	**(15,823)**	**(17,075)**	**(20,647)**	**(22,472)**	**(5,595)**	**(5,360)**	**(4,495)**	**(5,054)**	**(20,504)**	**(3,499)**	**(3,547)**	**(3,448)**	**(3,483)**	**(13,977)**	**(15,858)**	**(13,192)**	**216,935**	**422,681**	**600,807**	**662,479**
Other income (net)	8,143	11,522	11,805	12,510	16,661	4,215	4,054	3,669	3,619	15,557	2,400	2,061	2,000	2,000	8,461	8,000	8,000	7,000	7,000	6,000	5,000
Net income (pretax)	**(3,339)**	**(4,301)**	**(5,269)**	**(8,137)**	**(5,811)**	**(1,380)**	**(1,306)**	**(826)**	**(1,435)**	**(4,947)**	**(1,099)**	**(1,486)**	**(1,448)**	**(1,483)**	**(5,516)**	**(7,858)**	**(5,192)**	**223,935**	**429,681**	**606,807**	**667,479**
Net financial & tax	(1,991)	(187)	(1,098)	(2,760)	(1,276)	392	(2,459)	300	468	(1,299)	140	(1,599)	(250)	(250)	(1,959)	(1,200)	(1,000)	55,984	107,420	151,702	166,870
Net income	**(1,348)**	**(4,114)**	**(4,171)**	**(5,377)**	**(4,535)**	**(1,772)**	**1,153**	**(1,126)**	**(1,903)**	**(3,648)**	**(1,239)**	**113**	**(1,198)**	**(1,233)**	**(3,557)**	**(6,658)**	**(4,192)**	**167,951**	**322,261**	**455,105**	**500,610**
EPS basic	**(0.04)**	**(0.10)**	**(0.08)**	**(0.10)**	**(0.08)**	**(0.03)**	**0.02**	**(0.02)**	**(0.03)**	**(0.06)**	**(0.02)**	**0.00**	**(0.02)**	**(0.02)**	**(0.06)**	**(0.10)**	**(0.06)**	**2.31**	**4.21**	**5.67**	**5.94**
EPS diluted	**(0.04)**	**(0.10)**	**(0.08)**	**(0.10)**	**(0.08)**	**(0.03)**	**0.02**	**(0.02)**	**(0.03)**	**(0.06)**	**(0.02)**	**0.00**	**(0.02)**	**(0.02)**	**(0.06)**	**(0.10)**	**(0.06)**	**1.93**	**3.56**	**4.82**	**5.09**
Basic shares outstanding	34,638	41,589	49,235	52,762	53,354	56,190	57,339	58,154	58,451	57,616	61,216	62,215	62,277	62,339	62,011	66,079	69,383	72,853	76,495	80,320	84,336
Diluted shares outstanding	34,638	41,565	49,235	52,762	53,354	56,190	57,339	58,154	58,451	57,616	61,216	62,215	62,277	62,339	62,011	66,079	69,383	86,890	90,532	94,357	98,373

Source: SEC filings, company press releases, and ROTH Capital Partners

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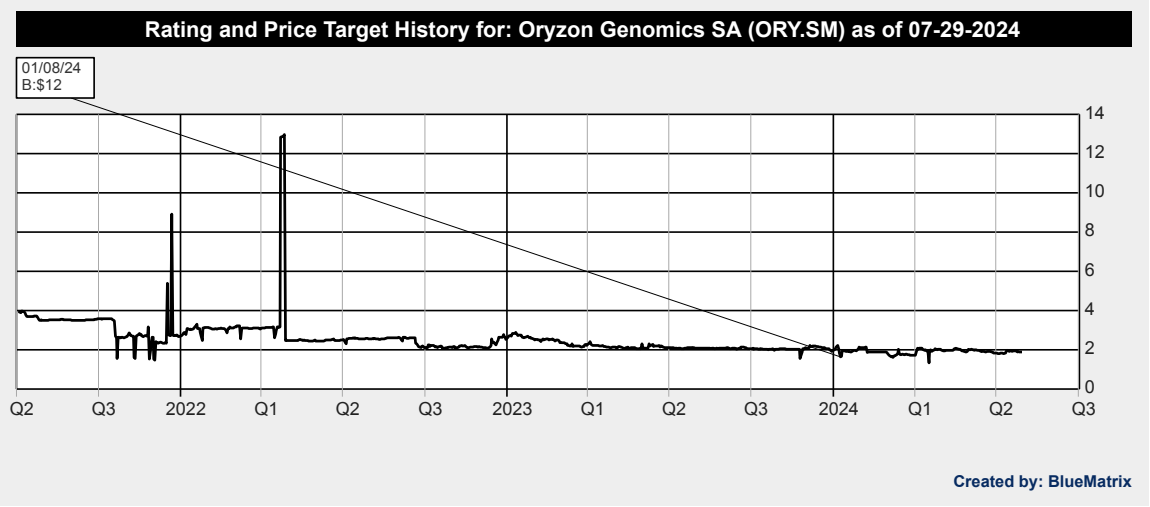
Disclosures:

Shares of Oryzon Genomics SA may be subject to the Securities and Exchange Commission's Penny Stock Rules, which may set forth sales practice requirements for certain low-priced securities.



Each box on the Rating and Price Target History chart above represents a date on which an analyst made a change to a rating or price target, except for the first box, which may only represent the first note written during the past three years. **Distribution Ratings/IB Services**shows the number of companies in each rating category from which Roth or an affiliate received compensation for investment banking services in the past 12 month.

Distribution of IB Services Firmwide

			IB Serv./Past 12 Mos. as of 07/31/2024	
Rating	**Count**	**Percent**	**Count**	**Percent**
Buy [B]	**354**	**73.44**	**86**	**24.29**
Neutral [N]	**77**	**15.98**	**4**	**5.19**
Sell [S]	**2**	**0.41**	**0**	**0**
Under Review [UR]	**48**	**9.96**	**1**	**2.08**

Our rating system attempts to incorporate industry, company and/or overall market risk and volatility. Consequently, at any given point in time, our investment rating on a stock and its implied price movement may not correspond to the stated 12-month price target.

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Neutral: A rating, which at the time it is instituted and or reiterated, that indicates an expectation of a total return between negative 10% and 10% over the next 12 months.

Sell: A rating, which at the time it is instituted and or reiterated, that indicates an expectation that the price will depreciate by more than 10% over the next 12 months.

Under Review [UR]: A rating, which at the time it is instituted and or reiterated, indicates the temporary removal of the prior rating, price target and estimates for the security. Prior rating, price target and estimates should no longer be relied upon for UR-rated securities.

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